ON THE DISCOVERY OF THE MYDRIATIC ACTION OF THE SOLANACEÆ.

BY

DR. RUD. KOBERT,

Professor of the History of Medicine and Pharmacology in Dorpat, Russia.

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On the Discovery of the Mydriatic Action of the Solanaceæ.

THERE can be no doubt that the discovery of the mydriatic action of certain solanaceæ was a matter of great importance for therapeutic practice. Nevertheless, there exists a singular uncertainty, if not confusion, as to the time of this discovery and as to the discoverer himself. In fact, there is not a single book published in German, French, or English, in which I can find reliable data in regard to this matter.*

In order to mend this defect, I beg leave to gather for a historical discussion all pertinent material, which, as may be presumed, is no light task.

The Greeks and Romans understood by mydriasis a condition of visual weakness, together with a dilatation of the pupil. This definition can be found in Paulus Ægineta (iii. 22),† Celsus (vi. 6), and Isagoges; and is

* The statements of A. Hirsch in the History of Ophthalmology (Graefe-Saemisch, Textbook of Ophthalmology, vol. vii. p. 235), appearing to be more trustworthy than those of other authors, have been adopted in the main in this paper.

† This interesting passage is rendered by Adams as follows: When the pupil does not appear changed in color, but much wider than natural, and when it sometimes wholly impairs the vision, and sometimes nearly so, and when every object appears smaller, the affection is called mydriasis. The cause of it is some redundant humor.

probably derived from the peculiar condition of visual weakness and pupillary dilatation invariably to be found in glaucoma. Some few authors, as Aëtius, designate improperly, also, other pathological conditions of the eye, such as phthisis bulbi, as mydriasis. In the presently accepted meaning—*i.e.*, dilatation of the pupils*—the word appears to have been first used by Cælius Aurelianus (Chron. ii., p. 344).

The first mention of a mydriasis produced by preparations of solanaceæ† we find in Galen's third volume of Methodus Medendi (Edit. Kühn, tom. x., Lipsiæ, 1825, p. 171). This author states in the second chapter of the quoted volume that grave visual interferences and mydriasis may result by a too intensive local application of drugs containing mandragora or hyoscyamus. Dioscorides and Plinius Secundus do not appear to have known anything of this action, at least these writers never mention it, while mydriasis itself occurs in Pliny, who even mentions an artificial production of mydriasis by the seeds of anagallis. Galen, therefore, is unquestionably the first author who refers to the mydriatic action of two species of solanaceæ. Still, his in every

* The word pupil, with its present signification, was used by Cicero (De Natura Deorum, ii. 57), who derives it from pupula, a little doll.

† The identification of the solanaceæ of the ancients is a difficult and as yet but partially-solved problem, *vide* Sprengel (Ped. Dioscorides de Mat. Med., Lipsiæ, 1829, pp. 602–605), Francis Adams (Paulus Ægineta, London, 1847, ii. pp. 218–19, and iii. p. 290), and Imbert Gourbeyre (Recherches sur les Solanum des Anciens, Paris, 1884). For our purposes it is of importance to know that all of the species in question have a mydriatic action.

way correct statement appears to have been wholly forgotten, for no subsequent writer ever speaks of this action, which fifteen hundred years later had to be discovered anew.*

In 1686, Dr. Ray, a famous English physician, reported in his Historia Plantarum (vol. i. p. 680) that a lady coming under his observation had placed upon a small ulcer beneath the eye a belladonna-leaf, and had afterwards been annoyed by an excessive dilatation of the pupil. Simultaneously the lady lost entirely the power of the pupil to react on light. The physician regarded this defect at first as a matter of accident, until a repetition of the belladonna application taught him that a dilatation of the pupil and loss of reactive power for several days were the physiological effects of belladonna.

But this second discovery also was again forgotten, although Ray's work was largely read. Thus, Boerhave (1668–1738), however familiar with medical literature, says in his book De Morbis Nervorum (p. 371), expressively that the juice of belladonna had no influence upon the eye, while Van Swieten, in his commentary of Boerhave's Aphorisms (vol. iii. p. 363), quotes Ray's case. And quite independently of Ray's observation, Evers reported in the *Berliner Sammlung*, 1773, vol. v. p. 565,† that he noticed in six

* Ebn, Baithar, and Paulus Ægineta, know positively nothing of this action.

† Gmelin states, in his General History of Vegetable Poisons (Nuremberg, 1777), p. 301, that already in 1765 he had noticed mydriasis as one of the symptoms of belladonna-poisoning, but he does not appear to regard this symptom as characteristic, but rather as an incidental one, for, in reviewing all symptoms, he omits this one.

persons hebetudo oculorum and dilatatio pupillæ as symptoms of the belladonna intoxication. Evers must accordingly be mentioned as the third discoverer of the mydriatic power of belladonna. Three years later the following case of poisoning occurred at Hamburg. A physician of repute, Dr. Reimarus, had ordered in a drug-store belladonna. The nephew of the apothecary, Johannes Andreas Daries (De Atropa Belladonna, Dissert. Inaug. Auctore Petro Joanne Andrea Daries. Lipsiæ, 1776. Reprinted in Ballinger's Sylloge, vol. ii. p. 58), who prepared the prescription from the fresh plant, had a drop of the juice of the berries, or of the herb, accidentally get into his right eye. Very soon after this accident he was troubled by mydriasis and considerable visual interferences. Reimarus, informed by letter of the druggist's trouble, wrote that he was aware that the ingestion of large quantities of belladonna produced mydriasis, but that he was surprised to learn that the external application of the drug could likewise produce this result. This was, however, Reimarus added, a very interesting matter, and invited decidedly to therapeutic trials of the drug in cataract operations. But even before the arrival of this letter, Daries ascertained, by experiments on a cat, that the fresh juice of the herb and of the berries of belladonna had actually a mydriatic power. Hence Daries is to be designated as the fourth discoverer of the mydriatic action of belladonna.

About the same time, or a little later, Doederlein* observed in his practice a case recall-

* Conrad Moench, Lehre von den Arzneimitteln,

ing that one of Ray mentioned above. A patient having placed a leaf of datura stramonium upon an ulcer near the eye, was soon affected with a complete paralysis of the pupil. Doederlein interpreted this mydriasis very correctly as the action of stramonium, and is accordingly to be regarded as the fifth discoverer of this action. Independently of him, Schiferli,* following the example of his preceptor Loder, who appears to have found the belladonna action for himself, used and recommended in 1796 an infusion of belladonna for cataract extraction. Loder is consequently the sixth discoverer of this action.

After this time the specific action of belladonna upon the eye became generally known in Germany and in other countries.

Thus, we find it mentioned as something generally known in Tromsdorf's Pharmacological Dictionary (Hamburg and Leipzig, 1802, vol. i. p. 299) The action of hyoscyamus was discovered by Himly in 1800 from botanical deductions, and was warmly recommended for ophthalmological purposes.† Ehlers,‡ one of his pupils, translated the publi-

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Marburg, 1795, p. 337. Moench, by the way, was quite familiar with the publications of Ray and Daries.

* Rud. Abraham Schiferli, Dissertatio de Cataracta, Jenæ, 1796; and Theoretical Practical Treatise on Cataract, Jena and Leipzig, 1797, p. 85. He was military surgeon, later professor of surgery, and died as such in Bern in 1837.

† Ophthalmolog. Beobachtungen und Untersuchungen, Bremen, vol. i. p. 1.

‡ De la Paralysie de l'Iris occasionée par Application locale de la Belladone, et de son Utilité dans le Traitement de divers Maladies des Yeux, par Himly, trad. par Emil August Ehlers, Paris, 1802.

cation of Himly in question into French, but, either on purpose or by mistake, always wrote belladonna instead of hyoscyamus, inducing thus the French physicians to employ belladonna therapeutically. In the second French edition, however, appearing 1803 in Altona, the word jusquiame is used instead of belladonna. In England, Paget* recommended the belladonna application for cataract extraction.

In lay circles, however, the mydriatic action of the solanaceæ was in the beginning of this century still wholly unknown, and was anew discovered by Runge, the discoverer of the aniline colors. This chemist makes, in his Chemischen Briefen,† the following interesting communication :

"In Jena I became soon acquainted with Döbereiner, and discussed with him my researches about vegetable poisons, especially the solanaceæ. Döbereiner appeared pleased with the methods instituted by me and the results of my investigations ; he constantly stimulated me to new researches. About this time I met Goethe, at the instigation of Döbereiner, who had told the poet that by experiments upon cats I had found a method of ascertaining with certainty whether or not a poisoning with stramonium had occurred. Goethe had thereupon expressed the desire to meet the young chemist, and to see the

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* *London Med. and Phys. Journal*, 1801, vi. p. 352; cf. *Edinburgh Med. and Surg. Journal*, 1813, ix. p. 279.

† This book is wholly unobtainable in the book market. A brief abstract of it appeared in the *Pharmac. Handelsblatt*, 1885, p. 23.

demonstration of his discovery. When I crossed the market square in the afternoon, dressed with a borrowed frock coat and stove-pipe hat, and carrying the cat under my arm, I created a universal sensation. The boys, who were loitering about the place, at the cry 'Doctor Poison!' suddenly came towards me, and surrounded me. To those joking at my fantastic appearance I said, 'Let me in peace. I am attending to some important business. I am going to Goethe.' I was instantly released. Coming to Goethe's house, I was led into the reception-room, and soon stood before the poet. His lofty, handsome, and powerful presence made such an overwhelming impression upon me, that, all in a tremble, I handed him the cat, as if I wanted thus to defend myself. 'Ah! So,' Goethe said, 'that's what is going to be the future terror of the poison-mixers. Just let me look.' I then turned the cat's head so that the light struck both eyes simultaneously, and the difference between the eyes could be readily seen. Goethe was greatly surprised. Alongside of the small slit in one eye, the round great opening in the other presented a very striking difference. In consequence of a somewhat large dose, the entire iris had almost become invisible, thus enhancing this singular aspect. 'How did you obtain this effect?' asked Goethe. 'With hyoscyamus, your excellency,' I answered. 'I have placed the unmixed juice of the pounded herb in the eye, therefore the action is so strong.' 'Döbereiner told me,' said Goethe, 'that both belladonna and stramonium act alike, and that you have ascertained that the active toxic princi-

ple is contained in the plant in all of its parts, from the root to the blossom, fruit, and seed. How is it with other plants, especially those of an affiliated relation?' 'A friend of mine, Dr. Carl Heise, induced by the peculiar action of the stated plants, has shown in an elaborate work that only the plants of the three orders mentioned above affect the pupils in a mydriatic manner. He has tried the action of innumerable other plants on the eye, and found them all to be inert save a few which produced the reverse of mydriasis, viz., a contraction of the pupil, such as aconitum.' 'Well,' Goethe said, 'there is a chance to discover the proper antidote for the toxic action of belladonna. Try this, and apply both antagonistic plants either simultaneously or one after another to the eyes of a cat. Observe the result. The matter is not without difficulties, but you will overcome these. But now, pray tell me, how you came to this peculiar kind of organic chemistry?'" Runge related: "In 1810 I was—a pastor's son, from the country near Hamburg—sent to Lübeck, and placed in the Rathsapotheke as an apprentice. It was a warlike time, and Napoleon prepared his invasion of Russia. All men able to carry arms were mustered out, and, on account of the universal unwillingness to serve under the tyrant, it was a matter of difficulty to find a substitute. Through recommendation of my uncle, I had received admission into several aristocratic families, and the son of one of them became a friend of mine. One evening he came to the drug-store in great commotion, and told me his trouble, that the day after to-morrow he had to present himself for

service, and that, being without physical defect, he probably would be taken. 'I would like to mutilate my hand,' he sighed, 'in order not to go into this ignominious war.' 'That is not necessary,' I said. 'Confide in me. I believe to be able to mutilate you for a short time with impunity. They will have to exempt you from service.' 'What are you going to do with me?' 'I will make you blind for twenty-four hours.' 'How are you going to do that?' 'Listen to me. About eight weeks ago I had to prepare a medicine, according to a doctor's prescription, in which a decoction of the juice of hyoscyamus was to be dissolved in water. Preparing the medicine in a mortar, a drop accidentally got into my eye. I experienced no pain, and did not observe any alteration until sensations of light flashes caused me to go to the looking-glass. How great was my astonishment when I saw the change that had taken place in my eye. The iris had almost wholly disappeared, and the eye looked precisely like that of a man suffering from amaurosis. The power of vision was also greatly weakened, as I noticed when I closed the unaffected eye. I don't know why this state of things did not raise any fears in me. After lasting a few days, the abnormal condition disappeared, the power of vision returned, and also the normal proportions of the iris, so that both pupils appeared again of equal size. And behold! such an affection I will produce in both of your eyes, and it would be very queer if you would not be discharged, even after a superficial examination.' After making some easily-removed objections, my friend consented to

this at that time very pardonable fraud, and thus saved his life, for of all men that went from Lübeck to the war in Russia but few returned. His temporary blindness lasted thirty-six hours, passed away painlessly, without leaving behind any deleterious results."

Thus far goes the report of Runge, from which we can distinctly see that he obtained the knowledge of the mydriatic action of the solanaceæ by the same accident as Daries derived his knowledge. Runge is consequently the seventh discoverer of this action. He tried even to practically utilize his discovery at once; for he recommended in his dissertation (De Novo Methodo Veneficium Dijudicandi, Jenæ, 1819) in a case of suspected atropine intoxication to place a drop of the urine of the poisoned person into the eye of a cat. The word atropine does not seem to have been known to Runge, for the solanacea alkaloid, isolated approximately by him, he calls koromegyn (Greek, magnifier of pupil). This alkaloid was isolated in 1830 properly by the apothecary Mein,* of Neustadt-Göders, and independently of him in 1832 by Geiger and Hesse,† while Liebig ‡ determined its chemical formula. The solution of the pure sulphate of atropine, instead of the extract of belladonna, was at once used by Geiger § and Hesse for the purpose of dilating the pupil. The named chemists succeeded soon ‖ after also in isolating hyoscyamine, the active principle of hyoscyamus. They showed that this alkaloid, like atropine, had a dis-

* Liebig's Annalen, vol. vi. p. 67.
† Ibid., vol. v. p. 38. ‡ Ibid., vol. vi., 1833, p. 66.
§ Ibid., p. 68. ‖ Ibid., vol. vii., 1839, p. 271.

tinctly mydriatic action even in a dilution of 1 to 1000.

In the majority of books treating of these historical facts, such as in Hirsch's History of Ophthalmology, and in Hirsch's Latest Discoveries of Materia Medica, Heidelberg and Leipzig, 1843, vol. ii. p. 160, we find the statement that the complete isolation of atropine and hyoscyamus occurred in the first half of the second decade of this century, and was obtained by Brandes and Runge. This, however, is wholly untrue.* For all those cases referred only to purified extracts but not to chemically pure alkaloids. After the mydriatic action of the solanaceæ alkaloids was positively made out, and had become generally known, their physiological *modus operandi* had to be determined.

Ernst Heinrich, as early as 1821, stated in his famous paper, De Motor Iridis (p. 102), that belladonna paralyzes the nerves of the muscular sphincter iridis. This view was confirmed by the experiments of Biffi (1845), Cramer and Ruiter (1853), and is now held exclusively by all ophthalmologists. Nevertheless, this view is only partially correct, for the most recent students of pharmacology have demonstrated that we have to deal here only with a paralysis of the peripheral ends of the nervus oculo-motorius, while the nervus sympathicus supplying the musculus dilator remains absolutely unaffected.

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* Equally erroneous is the statement that Reisinger (Bayerisch's Annalen; Abhandlungen aus den Gebiete der Chirurgie, Sulzbach, 1827; also *Salzburger Med. Chir. Zeitung*, 1825, No. 14, p. 237, and No. 15, p. 253) in 1824 had used the pure alkaloids of solanaceæ.

Fraser, of Edinburgh, discovered in 1861 the only practically applicable medium of pupillary contraction, viz., physostigmine or the extract of Calabar bean. Pilocarpine, muscarine, and nicotine likewise contract the pupil, but this contraction is in intensity and extent far inferior to that produced by physostigmine, and is of little practical importance.